

EFFECTS OF CHEMICAL STIMULATION OF THE CAROTID  
BODY UPON THE REFLEX CONTRACTION OF  
THE TIBIALIS ANTICUS MUSCLE

BY

WILLIAM KAUFMAN

*From the Physiology Laboratory, University of Michigan, Ann Arbor*

REPRINTED FROM THE AMERICAN JOURNAL OF PHYSIOLOGY  
Vol. 123, No. 3, September, 1938



## EFFECTS OF CHEMICAL STIMULATION OF THE CAROTID BODY UPON THE REFLEX CONTRACTION OF THE TIBIALIS ANTICUS MUSCLE<sup>1, 2, 3</sup>

WILLIAM KAUFMAN

*From the Physiology Laboratory, University of Michigan, Ann Arbor*

Received for publication May 26, 1938

Within recent years much emphasis has been placed on the effects of presso- and chemo-receptor reflexes initiated at the carotid sinus region on diverse types of physiological activity (Heymans et al., 1933). For the presso-receptors it has been found that endo-sinusoidal hypertension inhibits reflex activity of striated muscle and decreases muscle tonus; whereas, endo-sinusoidal hypo-tension has the reverse effects (Tournade and Malmejac, 1929; Koch, 1932; Spsychala, 1932; Mies, 1933; Heymans and Bouckaert, 1933; Tournade and Rocchisani, 1934). However, no analysis of the changes in reflex activity in response to chemo-receptor stimulation has come to our attention.

**EXPERIMENTAL PROCEDURE.** Dogs anesthetized with morphine (2 mgm./kgm.) and urethane (1 gm./kgm.) at a depth just sufficient to abolish the corneal reflex were used. The vago-sympathetic trunks were isolated for cold block. The trachea was connected directly to a system of rebreathing tanks designed to absorb carbon dioxide. Respiration was recorded by a spirometer directly connected with the rebreathing tanks; in addition, costal and abdominal respiratory movements were separately registered with the band pneumograph of Moyer and Gesell (1935). The latter procedure permits the registration of respiratory movements during pneumothorax. Down-stroke signifies inspiration; up-stroke, expiration.

With the exception of the internal carotid and the occipital arteries, the efferent vessels of the bifurcation of the common carotid artery were tied and cut between double ligatures, care being taken that Hering's nerve and the circulation to the carotid body were not injured. The lingual artery was cannulated so that backward intra-arterial injections could be made into the left innervated carotid body region. The cannula was

<sup>1</sup> A preliminary report of this paper appeared in the Proceedings of the American Physiological Society (1936), page 89.

<sup>2</sup> These experiments were supported in part by a grant from the Rockefeller Foundation to Robert Gesell for studies on respiration.

<sup>3</sup> A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.



stitched to the adjoining muscular tissue to minimize mechanical stimulation of the carotid sinus region during backward intra-arterial injections. The right carotid body region was similarly dissected, but only after Hering's nerve had been identified and severed, and the internal carotids, occipital arteries, bifurcation of the common carotid artery, and common carotid artery (for a distance of 3 cm. below the bifurcation) stripped of their fascial investment. With this arrangement it could be determined whether or not changes in reflex contractions were of central or reflex origin.

The left sciatic nerve was isolated in the thigh; the branches to the hamstrings cut; the posterior tibial nerve identified, severed, and the central end placed on shielded electrodes of special design. Skin flaps were closed around the outer jacket of the shielding. The electrodes were connected to the secondary coil of an inductorium whose primary received the discharge from a thyatron stimulator. After immobilization of the left leg, the tendon of the tibialis anticus muscle was freed for a distance of about 6 cm. above its insertion, and connected by means of ligature to an isotonic spring-tension myograph. A slight constant tension was exerted on the muscle throughout the experiment. A fall of the base line of the reflex contractions indicated a decrease in the muscle tone; a rise, the converse. Freshly prepared solutions of  $M/20$  sodium sulfide and  $M/100$  sodium cyanide in 0.9 per cent saline diluted as necessary in normal saline were injected.

**RESULTS.** Backward intra-arterial injection (fig. 1, *F* and *C*) of 1 cc. of  $M/500$  sodium cyanide or  $M/40$  sodium sulfide (average injection time, at uniform rate, one second) into the innervated carotid artery produced noticeable changes in respiration, blood pressure, heart rate, and reflex contraction of the tibialis anticus muscle. Injections of 1 cc. of  $M/100$  sodium cyanide or even of 1 cc. of  $M/20$  sodium sulfide into the denervated sinus produced no changes. Control injections of 1 cc. of physiological saline into the innervated and denervated carotid sinus regions caused no perceptible effects. Since sodium cyanide and sulfide seemed to cause identical modifications in blood pressure, heart rate, etc. (fig. 1, *F* and *C*), sodium cyanide was used exclusively as the stimulating agent.

For economy of space, the phrase "stimulation of the chemically sensitive endings of the carotid body" has been shortened to "chemical stimulation"; "submaximal reflex contraction amplitude of the tibialis anticus muscle" has been shortened to "amplitude" or "reflex amplitude."

*Modifications in the reflex amplitude.* By varying the frequency of reflex stimulation through a range increasing progressively from 36 stimuli per minute to a value high enough to produce reflex tetanus, it was possible in most animals to obtain, as a result of chemical stimulation, a gamut of changes in the reflex contraction of the tibialis anticus muscle. For exam-

ple, at the rate of 36 reflex contractions per minute, in a naturally ventilated animal with intact vagi, chemical stimulation gave a diminution or no detectable decrease in the amplitude or tone. At the rate of 83 per minute (fig. 1, *B*), chemical stimulation caused a diminution in muscle tone together with a slight increase in the reflex amplitude. At 205 stimuli per minute (fig. 1, *G*), where a partial reflex tetanus had been established, chemical stimulation caused a greater reduction in the reflex tone with an associated increase in the amplitude of the discrete reflex contractions. Simultaneously undulatory changes in both tone and amplitude having a definite respiratory rhythm also appeared. With rates high enough to give reflex submaximal tetanus (fig. 1, *H*), chemical stimulation caused an abrupt, somewhat notched fall in the plateau. That this fall was not due to fatigue is shown by its absence in the plateau of reflex tetanus maintained for longer period without chemical stimulation. The latent period of the onset of alterations in tonus and reflex amplitude are similar to those of the corresponding hyperpnea and the duration of these changes (in all but the reflex submaximal tetanus) and the duration of the hyperpnea following chemical stimulation are of the same order.

Comparable results were obtained in vagotomized animals subjected to constant pulmonary ventilation during bilateral pneumothorax (fig. 1, *I, J, K, L, M*). At 180 twitches per minute, chemical stimulation produced two types of pronounced undulatory groupings in the reflex contractions which were independent of the rhythm of the artificial ventilation pump and related closely to the phases of respiratory movements. When at this rate there was no evidence that partial reflex tetanus existed, rhythmic changes occurred only in the reflex amplitude with the points of maximal amplitude at the beginnings of inspiration (fig. 1, *L*), the lowermost points at the beginning of expiration. However, when partial tetanus existed at this rate (fig. 1, *K*), fairly constant increased amplitudes accompanied wave-like tonic changes in which the crest occurred during inspiration and the trough corresponded to the beginning of expiration. At 390 reflex twitches per minute (fig. 1, *L*), the respiratory rhythm following chemical stimulation was less precisely defined than that for 180 stimuli per minute. In the pre- and post-stimulation portions of the records of reflex contraction at rates of 180 and 390 per minute, there is no hint of a respiratory rhythm in the configuration of the reflex twitches. These results before and after vagotomy classified in group one are by far the most representative.<sup>4</sup>

A sub-group of two animals merits special attention. Here, chemical

<sup>4</sup> In this particular animal with reflex submaximal tetanus (fig. 1, *M*), chemical stimulation produced a sharp stepwise rise (usual response, fall) in the plateau of reflex submaximal tetanus which is tentatively considered as "rebound" from an inhibitory volley.



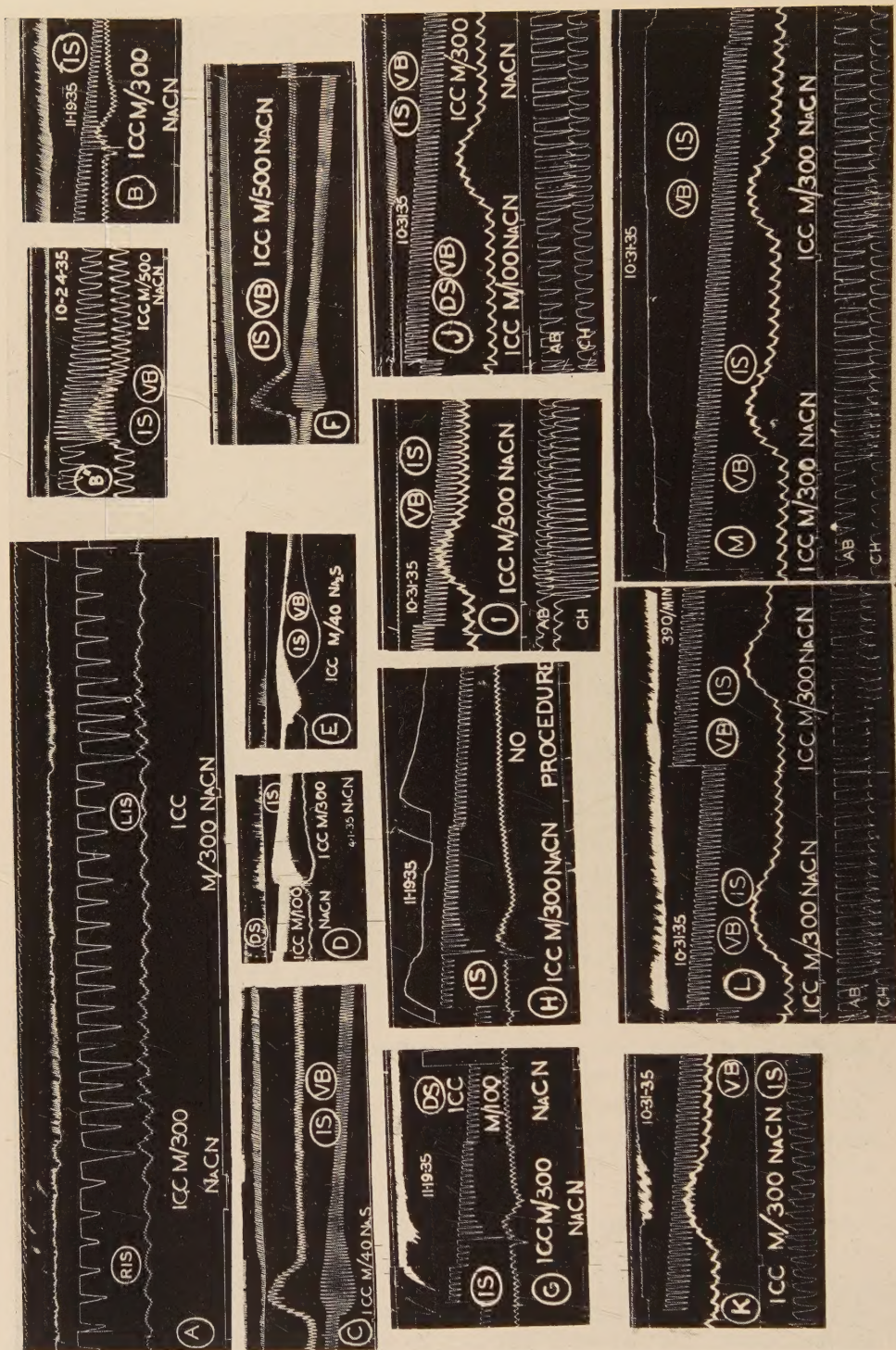


Fig. 1



stimulation caused either a complete suppression of reflex contractions or else a marked decrease in reflex amplitude with little or no diminution in tonus with stimulation at frequencies of 36, 72, 90, and 132 per minute



Fig. 2

Figs. 1 and 2. *IS* = injection into intact carotid sinus; *DS* = injection into denervated carotid sinus; *RIS* = injection into right intact carotid sinus; *LIS* = injection into left intact carotid sinus; *VB* = vagi blocked; *IV* = intravenous injection; *AB* = abdominal respiratory movements; *CH* = thoracic respiratory movements.

(fig. 2, A, B; fig. 1, B''). But when the rates increased beyond these values (fig. 2, C, D), the previously described diminution in muscle tonus occurred with either a diminution, no change, or actual augmentation of the reflex

amplitude, provided that the highest frequency producing discrete reflex muscle twitches was not exceeded. These results were obtained with the vagi intact or cold-blocked, with the animal normally or artificially ventilated. Carotid body stimulation produced in one of these animals notched depressions in the plateau of submaximal reflex tetanus (fig. 2, *H*). The notches occurred just prior to and practically synchronous with the beginning of each expiration.

Some animals, in the absence of experimental procedures, exhibited a well or poorly defined spontaneous respiratory rhythm of reflex amplitudes and of muscle tone. However, the changes in muscle tone were more regular than those of amplitude (fig. 1, *A*). The lowermost portion of the trough of the tonus wave coincided with the beginning of expiration; the beginning of inspiration fell on the descending portion of the tonus wave in advance of the point synchronous with expiration. The reflex amplitudes were lowest at the latter part of inspiration. In these animals, chemical stimulation intensified the first tonus wave by an exaggeration of all phases previously described (even to suppression of individual reflex contractions during inspiration) then reduced the tone, completely obliterating the undulatory base-line so prominent during the pre-stimulation period and simultaneously augmented the reflex amplitude.

In ten animals we were unable to show effects of chemical stimulation on reflex contraction. In three animals the tibialis anticus reflex could be elicited only with intense stimuli and following chemical stimulation no changes in reflex amplitude or muscle tone could be found. In seven dogs, the functional state of the vagi appeared to influence the changes resulting from chemical stimulation (King, Garrey and Bryan, 1932). In four of these animals changes in the reflex following chemical stimulation obtained only after the vagi were cold-blocked (fig. 1, *E*), the most typical findings being a poorly sustained, often abrupt, increase in the amplitude unaccompanied by tonic changes which occurred 10 to 30 seconds after the injection of sodium cyanide. In one animal subsequent to chemical stimulation there was a slight diminution both of the reflex amplitude and muscle tone (fig. 1, *C*, *F*) which was followed by a return of the tone to the pre-stimulation level and a long sustained period of increased reflex amplitude; further chemical stimulation reproduced these changes upon a background of higher reflex amplitudes. In two dogs subsequent to chemical stimulation, changes in the reflex amplitude occurred only when the vagi were functionally intact (fig. 1, *D*). Here the same latent period was occasionally observed both for the hyperpnea and the increased reflex amplitude (unaccompanied by tonic changes) following chemical stimulation; however, more often the latent period was one and a half to two times that of the accompanying hypernea. In these ten animals only the effects of chemical stimulation on the slow rates of reflex contraction were investigated be-



cause at the time these animals were studied the importance of frequency of the elicitation of the reflex twitch in relation to the alteration brought about by chemical stimulation was not realized. Furthermore, without exception, constant pulmonary ventilation was not employed in the study of these animals. In subsequent studies throughout which higher rates of reflex elicitation were employed, only two animals were encountered in which the effects of chemical stimulation on reflex contraction depended on the functional state of the vagi. These animals were very unstable and died soon after the experiment had begun.

*Crossed nervous pathways.* Chemical stimulation of the homo- or hetero-lateral carotid glands was equally effective in producing changes in the reflex contraction, indicating that the final central pathways mediating the changes in reflex contractions are composed of approximately equal numbers of crossed and uncrossed fibers (fig. 1, A).

*Effects of changes in the systemic blood pressure.* Since chemical stimulation produces variations in mean systemic blood pressure, capable of causing alterations in reflex contractions and tonus of striated musculature (Koch, 1932; Spychala, 1932; Mies, 1933), and since urethane anesthesia or any deep anesthesia abolishes tonus changes through pressoreceptor reflexes our findings are related to the chemoreceptor stimulation only. This is supported by direct observation (see fig. 2, B, D; and fig. 2, A, C). In the first there is a rise and in the second a marked fall in pressure with no change in the reflex contraction in either. The method of Moissejeff (1927) in which the existing endo-sinusoidal pressures could be varied mechanically was also tried with the same result. Even doubling endo-sinusoidal pressure had no recognizable effect on reflex contraction despite the large fall in the systemic blood pressure. Elevation of the systemic blood pressure by intravenous injections of adrenalin (fig. 2, F, G) and occlusion and deocclusion of the common carotid arteries were without effect. Furthermore, vagal stimulation adequate to bring about cessation of the heart beat with a consequent fall of mean blood pressure to zero, produced no changes in reflex contractions.

**DISCUSSION AND CONCLUSIONS.** The changes in amplitude and tone of the tibialis anticus muscle can be explained upon a uniform basis, if one accepts that such stimulation causes showers of inhibitory nerve impulses to converge by crossed and uncrossed fiber tracts upon the anterior horn cells of the spinal cord, and that the inhibitory streams thus produced manifest themselves against a suitable background of excitation (Sherrington, 1906; Creed et al., 1932). To test the validity of this hypothesis let us first consider the tracing in which inhibition was pitted against reflex twitches of low frequencies (fig. 2, A, B, C, D, H; fig. 1, B''). It is assumed that immediately preceding chemical stimulation, the c.e.s. which causes contraction is built up in response to each electrical stimulus. Superposed

on these contractions, chemical stimulation caused an inhibitory barrage of nerve impulses to descend the spinal cord sufficient to inactivate part or all of the c.e.s. When no further inhibitory impulses descended in inactivating amounts, the c.e.s. within the motoneurons of the tibialis anticus muscle could build up once more to the nervous discharge level with the concomitant reappearance of reflex twitches. Diminution in the amplitude signifies that c.i.s. was produced in amounts great enough to prevent c.e.s. from reaching a threshold value in only a portion of the motoneurone field which responds to each shock of the stimulator.

When the rate of submaximal reflex contractions is increased, not only is the c.e.s. within the motoneurons built up at a faster rate, but also repetitive firing becomes a prominent feature. Although each stimulus to the afferent nerve still gives discrete reflex twitches, the degree of summation of the after-discharge often causes a considerable rise in the base line of the isotonic reflex contractions. At this stage the inhibition resulting from the chemical stimulation is most effective principally in the prevention of after-discharge. If the c.i.s. is strong enough, there is produced in addition to cessation of repetitive firing a decrease in the reflex amplitude due to inhibition of a portion of the previously active motoneurons. When this happens there is a diminution in amplitude upon a lowered tonic base line (fig. 2, *A, B*). With higher rates of stimulation (fig. 2, *C, D*; fig. 1, *G*), only the after-discharge is successfully inhibited because the waxing c.e.s. produced by the afferent excitatory volley is powerful enough to overcome the prevailing c.i.s. produced by chemical stimulation so that in response to this chemical stimulation there is either no change or more often an increase in the reflex amplitude upon a lowered tonic level.<sup>5</sup>

As far as we have been able to determine with control procedure, the effects of carotid body stimulation are in no way related to fatigue or

<sup>5</sup> The usual signs of inhibition following chemical stimulation were absent in more than 10 per cent of the animals in which under natural ventilation the effects of this stimulation were investigated at low rates of reflex contraction. This is not surprising since the effects of chemical stimulation cannot be demonstrated in most animals at these low rates of stimulation. However, in a portion of these animals increased reflex amplitudes were obtained in response to chemical stimulation after the vagi were blocked. This increased amplitude might have been caused by: 1, the blowing off of carbon dioxide; 2, increased sensitivity of the anterior horn cells in the vagotomized animal to excitatory stimuli; 3, the co-existence of visceral nervous factors such as those caused by a bladder distended with urine which makes its presence felt only after vagal block. Two naturally ventilated animals responded to chemical stimulation at low rates of reflex elicitation with increased amplitudes only when the vagi were intact; here it was felt that the blowing off of carbon dioxide was an important factor. No further statement concerning these animals is made. It is felt that the validity of the conclusions previously drawn on the basis of the behavior of the majority of animals is in no wise affected by the response of this smaller group to chemical stimulation.



volume flow of blood through cord or muscle. Complete inhibition of the heart for twenty seconds, or occlusion of the abdominal aorta as long as ten minutes caused no changes in reflex amplitude or tonus resembling those of chemical stimulation. Changes in tibialis anticus contraction must then be due to a reflex modification of the reflex process.

Irradiation from the respiratory center is a well recognized phenomenon as witnessed in the respiratory fluctuation of heart rate and blood pressure and of the knee jerk. Evidence points that this irradiation increases with the intensity of the respiratory act; for example, carotid body stimulation frequently gives rise to respiratory grouping of reflex contractions otherwise absent (fig. 1, *K, L*). These groupings are unrelated to the excursions of the lungs for in artificial respiration during pneumothorax they are in phase with the natural respiratory act. The groupings were more clearly defined during the deep breathing of vagal block (fig. 1, *K*) which is in agreement with the findings of Adrian, Bronk and Philips (1932) and King, Blair and Garrey (1931) (fig. 1, *L*; fig. 2, *H*). At rates high enough to produce reflex submaximal tetanus, chemical stimulation in some of the animals gave rise to descending inhibitory streams strong enough to inhibit this tetanus.

We come now to the relation of our findings to respiration. The carotid body is admittedly an organ of respiratory control which drives the respiratory center when oxidations are impaired. It accomplishes this end by increasing the rate of build up of the c.e.s. of the respiratory neurones thus increasing both rate and depth of breathing (Gesell, Steffenson and Brookhart, 1937). Excitation of the carotid body with sodium cyanide, if properly timed, is capable of augmenting a normal inspiration already on its way. A slightly later injection will augment an expiratory act (Gesell and White, 1937). This shows its direct connection with the respiratory mechanism. We now find that it is connected with motor system as a whole by its inhibitory action on the non-respiratory muscles. This reciprocal action of the chemoceptor organs raises the interesting speculation that they may play a part in respiratory control, particularly under conditions of stress, by giving precedence to respiratory reflexes.

#### SUMMARY

Effects of local excitation of the carotid body with sodium cyanide sufficient to cause marked augmentation of breathing, were studied on the reflex contraction of the m. tibialis anticus of the dog.

Such excitation at times reduced the amplitude of individual reflex contractions elicited at a low frequency of stimulation.

This same inhibitory action was more uniformly demonstrated on reflex and tonic contraction provoked by a higher frequency of stimulation.

These effects were not due to carotid sinus reflexes or to associated

changes in volume flow of blood or to fatigue. Their onset was synchronous with associated changes in breathing. They are tentatively explained on the assumption that descending inhibition interacts with the c.e.s. built up in the motor neurones of the tibialis anticus as a result of reflex stimulation.

It is suggested that the reciprocal action of the chemoceptors in building up c.e.s. in the respiratory neurones and in neutralizing c.e.s. in the neurones of the non-respiratory muscles may play a part in the control of breathing by giving precedence to respiratory reflexes. This may be an important factor during respiratory distress.

The writer wishes to thank Dr. Robert Gesell for his valuable suggestions and for his help.

#### REFERENCES

- ADRIAN, E. D., D. W. BRONK AND G. PHILIPS. *J. Physiol.* **74**: 115, 1932.  
 CREED, R. S., D. DENNY-BROWN, J. C. ECCLES, E. B. T. LIDDELL AND C. S. SHERRINGTON. Reflex activity of the spinal cord. Oxford, at the Clarendon Press, 1932.  
 GESELL, R. AND C. MOYER. *Quart. J. Exper. Physiol.* **24**: 315, 1935.  
 GESELL, R., E. H. STEFFENSEN AND J. M. BROOKHART. *This Journal* **120**: 105, 1937.  
 GESELL, R. AND F. WHITE. In press.  
 HEYMANS, C. AND J. J. BOUCKAERT. *Presse Med.* **36**: 731, 1933.  
 HEYMANS, C., J. J. BOUCKAERT AND P. REGNIER. *Le Sinus Carotidien et la Zone Homologue Cardio-aortique*. G. Doin et C.  
 KING, C. E., E. A. BLAIR AND W. E. GARREY. *This Journal* **97**: 329, 1931.  
 KING, C. E., E. A. BLAIR AND W. R. BRYAN. *This Journal* **102**: 305, 1932.  
 KOCH, E. *Ztschr. f. Kreislaufforsch.* **24**: 251, 1932.  
 MIES, H. *Ztschr. f. Biol.* **94**: 108, 1933.  
 MOISSEJEFF, E. *Ztschr. f. d. ges. exper. Med.* **53**: 696, 1927.  
 SHERRINGTON, C. S. *The integrative action of the nervous system*. New Haven: Yale University Press, 1906.  
 SPYCHALA, V. *Ztschr. f. d. ges. exper. Med.* **83**: 203, 1932.  
 TOURNADE, A. AND J. MALMEJAC. *Compt. rend. Soc. de Biol.* **110**: 708, 1929.  
 TOURNADE, A. AND L. ROCCHISIANI. *Compt. rend. Soc. de Biol.* **115**: 1117, 1934.





